**Author’s response to reviews**

**Title:** Effects of valproic acid on skeletal metabolism in children with epilepsy: a systematic evaluation and meta-analysis based on 14 studies

**Authors:**

Li Min (limin556688@aliyun.com)

Wang Chunyan (asimipy@sina.com)

Rong Biaoxue (research568rbx@yeah.net)

**Version:** 1  **Date:** 23 Oct 2019

**Author’s response to reviews:**

BPED-D-19-00413

TI: “Effects of valproic acid on skeletal metabolism in children with epilepsy: a systematic evaluation and meta-analysis based on 14 studies.”

Dear Dr. Pierluigi Marzuillo:

Our manuscript has been carefully revised according to the reviewers’ suggestions and also revised according to the preferred format for the journal. The manuscript has been professionally edited for English language readability prior to resubmission to the journal. We have taken all of the comments of the two reviewers into account and wish to respond as follows:

**Part A: COMMENTS OF REVIEWER #1**

Question (1): The methods would appear to describe the statistics used in analysis well, however there are gaps overall. The inclusion and exclusion criteria use 6 months of valproic acid as a necessary factor, however it is not clear at all the timeline on which all of the blood values were done. Were they compared on the same timeline? Ie did all of the studies included use 6 months as the time for testing? Or were there studies that used shorter or longer windows? In the Extraction of Study Variables section, "...and (5) 18 Key detection data on bone metabolism indicators: calcium, serum phosphorus, ALP, PTH, 19 osteocalcin, 25-OH-VitD and BMD..." is stated but nil about when in follow up these were done.

Answer: On the inclusion criteria, uniform standards are applied to each study. Patients enrolled in the study must have used valproic acid for more than 6 months. The included studies must include at least one of the following indicators: serum calcium, phosphorus, alkaline phosphatase (ALP), parathyroid hormone (PTH), osteocalcin, and 25-hydroxy-vitamin D (25-OH-VitD) and bone mineral density (BMD). These explanations are showed on page 4, line 8 to 13, highlighted in blue.
Question (2): There is no mention of looking at any control group in the body of the study, however Figures 2, 4 and 5 mention control groups. All of the studies were retrospective, did they all have control groups? How many of the 14 did?
Answer: Each study included in this meta-analysis was set up in the control group, and the control group consisted of healthy children with physical examination. The explanation is showed on page 4, line 9 to 10, highlighted in blue.

Question (3): As it is not clear what exactly the timeline is, and there is some clarity needed on the statistics, the only part of the conclusion that is sure is the statement re the need for more study.
Answer: Children who took valproic acid for more than 6 months can be enrolled. After the group is enrolled, blood is taken for testing. The children in the control group were enrolled and blood was taken for testing. These explanations are showed on page 4, line 8 to 23, highlighted in blue.

Question (4): The english grammar needs a considerable amount of work, there is misuse of the, it, on, in etc in much of this paper, there is awkward language that makes it difficult to read, the tense is inconsistent, sometimes present, sometimes past, and there are spelling mistakes.
Answer: As suggested by this reviewer, the manuscript has been carefully revised regarding a standard writing format and grammar. Our manuscript has been polished by native English speakers. We are also very grateful to the reviewer for the positive comments on our manuscripts.

Part B: COMMENTS OF REVIEWER #2
Question (1): Thank you for the opportunity to review your manuscript. There are necessary grammar and language edits that you may need assistance with.
Answer: As suggested by you, the manuscript has been carefully revised regarding a standard writing format and grammar. Our manuscript has been polished by native English speakers. We are also very grateful to the reviewer for the positive comments on our manuscripts.

Question (2):
Abstract: Background: delete 'some... to evaluate ..... Answer: We have made changes based on your suggestions. These changes are showed on page 2, line 2 to 5, highlighted in blue.

Question (3):
Introduction:
Of these, ...... as an AED and mood .... Growth ...... with epilepsy is a dynamic .... status, including bone ...
Delete 'study shows that'
Bone conversions?
To investigate whether it acts as ... disorder, multiple studies have been performed. WE colelcted ...... acid.
Answer: We have made changes based on your suggestions. These changes are showed on page 3, line 3 to 4, 7 to 8, and 10 to 16, highlighted in blue.

Question (4):
Methods:
.... Science from the start ....
Answer: We have removed this unnecessary statement.
Question (5):
Inclusion:
1. Children with epilepsy classified by the international ....
Answer: We have made changes based on your suggestions. The changes are showed on page 4, line 6 to 7, highlighted in blue.

Question (6):
Exclusion:
Delete 'must be excluded' in #1, 'Except valproic acid' #3, 'the patient's' # 5
Answer: We have made changes based on your suggestions. The changes are showed on page 4, line 16 to 18, and 20, highlighted in blue.

Question (7):
Quality: Delete 'using the tool' 2nd line
A star is awarded ...... qualified such that the ...... 
..... disagreement, a third expert was invited to ....
Answer: We have made changes based on your suggestions. The changes are showed on page 5, line 7 to 8 and line 10 to 13, highlighted in blue.

Question (8):
Stats:
.... indicating low risk of heterogeneity
Delete 'to perform the analysis'
Answer: We have made changes based on your suggestions. The changes are showed on page 5, line 18 to 19 and line 22 to 23, highlighted in blue.

Question (9):
Results:
Delete 1st header
Of the initial 198 studies, 88 were inconsistent with inclusion criteria ( ......). Of the remaining 110, 71 were excludued ( ..... . ). Of the remaining 39, 25 were excluded.
Answer: We have made changes based on your suggestions. The changes are showed on page 6, 9 to 12, highlighted in blue.

Question (10):
2nd paragraph:
Studies ranged in size from 37 - 126 cases with 467 .... . Boys accounted for ...... in the valproic acid and ........ control groups respectively.
Delete 'summary analysis revealed' ..... with no differences ....
Answer: We have made changes based on your suggestions. The changes are showed on page 6, line 17 to 21, highlighted in blue.

Question (11):
Quality
... retrospective .... orginated from
What do you mean with same exposure factors?
receeeved rather than got .... stars
Answer: We have made changes based on your suggestions. The changes are showed on page 7, line 1, 2, 5 and 6, highlighted in blue.
Question (12):
Heterogeneity
Accordingly, we used the random...to complete analysis.
...results showed......which indicates no heterogeneity
Answer: We have made changes based on your suggestions. At the suggestion of another reviewer, we put this part of the subsection of the meta-analysis.

Question (13):
For result paragraphs, be consistent and list CI in ( )
Answer: We have made changes based on your suggestions. The changes are showed on page 7 to 9, highlighted in blue.

Question (14):
Discussion
...such as personal disease, drugs......traditional agents
...system, followed by multi-disciplinary investigations
....but results are inconsistent
Answer: We have made changes based on your suggestions. The changes are showed on page 9, line 23 and page 10, line 3 to 5, highlighted in blue.

Question (15):
2nd paragraph:
Our analysis included 14 studies with good......quality. Delete next 2 sentences - duplication of methods
Delete 'due to different opinions' sentence
...confirm this finding
Answer: We have made changes based on your suggestions. The changes are showed on page 10, line 8 to 9, highlighted in blue.

Question (16):
3rd:......which implies that
Start DEXA as new paragraph
Delete 'in other words'
...and affect bone structure
Answer: We have made changes based on your suggestions. The changes are showed on page 10, line 21 and page 11, line 15, highlighted in blue.

Question (17):
5th: Quality evaluation showed good homogeneity. N-O should be uppercase 1st letter
received rather than reached...stars
Start new paragraph: Delete 'In summary' sentence, start 'Limitations
Answer: We have made changes based on your suggestions. The changes are showed on page 11, line 19, 20 and 22, highlighted in blue.

Question (18):
Acknowledgements: Did you mean reviewers rather than interviewers?
Answer: We have made change based on your suggestions. The change is showed on page 13, line 1, highlighted in blue.
Question (19): Figure legends: shorten throughout

1: After screening, 14 ..... 
...suggesting moderate ....

3: A and B. Valproic acid did not ......

4: A and B: Osteocalcin ... epilepsy was not affected by use of valproic acid

Answer: We have made change based on your suggestions. The changes are showed on page 17, highlighted in blue.

Part B: COMMENTS OF REVIEWER #3

Question (1): Is the study design appropriate for the research question (considering whether the analyzed population accurately reflects the design and whether you see any problems with control/comparison groups, e.g., likely confounders)?

No - there are minor issues

Answer: Thank you very much for your recognition of our work. We have further explained the statistical design and implementation.

Question (2): Are methodologies adequate and well implemented (considering whether assumptions are addressed and whether analyses are robust)?

Yes - methodologies are adequate and well implemented, assumptions are addressed, analysis is robust

Answer: Thank you very much for your recognition of our work.

Question (3): Are the analyses adequately communicated (considering whether reporting details are adequate and whether figures and tables are well labeled and described)?

No - there are minor issues

Answer: The idea and implementation of statistics have been described in detail in the relevant sections.

Question (4): Does the interpretation accurately reflect the analyses without overstatement (considering whether limitations/bias are acknowledged and whether accurate descriptors, e.g., 'significant', are used)?

Yes - interpretation accurately reflects analyses, limitations/bias are acknowledged, accurate descriptors are used

Answer: Thank you very much for your recognition of our work.

Question (5): Could an appropriately REVISED version of this work represent a statistically sound contribution?

Probably - with minor revisions

Answer: Thank you very much for your recognition of our work. We have further explained the statistical design and implementation.

Question (6): The authors performed a systematic review and meta-analysis according to PRISMA statement. Overall, the study is performed well and there is no flawed mistake. The study has sufficient steps according to PRISMA statement, including searching, screening, data extraction, quality assessment, and data analysis. The authors used a relevant scale (the Newcastle-Ottawa Scale) to assess the quality of included studies and sufficient statistical analysis methods. However, the statistical method should
be clarified more about the sensitivity analysis. In addition, the authors should not combine different outcome in a meta-analysis (figure 2, 3, 4, and 5).
Answer: We added the content of the sensitivity analysis. The changes are showed on page 5, line 22 to 23, page 6, line 1, highlighted in blue. Because of the large number of images, we merged the forest maps of the meta-analysis. This is mainly for the reader to quickly access the information of this study.

REQUESTED REVISIONS:

I hope these below comments could make this manuscript better:

1- In the abstract, the authors should report the effect size (SMD and 95% CI) along with (or instead of) the p-value.
Answer: We did not describe this data in the abstract, mainly because of the limitation of the number of abstract words. If we add these data, the length of the abstract will be very long. In any case, these data are well represented in the corresponding parts of the text.

2- In the statistical analysis section, the sensitivity analysis should be clarified more, eg which method was used to perform the sensitivity analysis.
Answer: We added the content of the sensitivity analysis. The changes are showed on page 5, line 22 to 23, page 6, line 1, highlighted in blue.

3- In the results section, the heterogeneity test section might be added to each of the outcomes analysis, instead of separating into a section.
Answer: We have made changes based on your suggestions.

4- In figure 2, 3, 4 and 5, there should be no "overall" result from meta-analysis. These 8 outcomes should be analyzed separately.
Answer: Because of the large number of images, if we make these pieces into a single image, the number of images will exceed 15. So we merged the forest maps of the meta-analysis. However, we removed the "overall" result from the image.

5- There are several typos needed to revise.
Answer: As suggested by this reviewer, the manuscript has been carefully revised regarding a standard writing format and grammar. Our manuscript has been polished by native English speakers. We are also very grateful to the reviewer for the positive comments on our manuscripts.

We would like to extend thanks to all of the reviewers and to the editing staff at ‘BMC Pediatrics’ for this opportunity to resubmit a revised version of our work. We would like to express our great appreciation to you and reviewers for the manuscript comments and suggestions. We look forward to hearing from you, and, as before, please address all communications regarding this manuscript to myself as the corresponding author.
Rong Biaoxue, Department of Medicine, Shenmu Hospital, Shenmu, 719300, Yulin City, Shaanxi, China. Tel: +86 15349260656. E-mail: research568rbx@yeah.net